UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/072,425	02/07/2002	Muriel Moser	DECLE55.1C2CD1	4226

21874 7590 04/21/2009

EDWARDS ANGELL PALMER & DODGE LLP
P.O. BOX 55874
BOSTON, MA 02205

EXAMINER	
EWOLDT, GERALD R	
ART UNIT	PAPER NUMBER
1644	
MAIL DATE	DELIVERY MODE
04/21/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/072,425	MOSER ET AL.	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-7,9,34,35,42,46,50,54,58-62 and 64-66* is/are pending in the application.

4a) Of the above claim(s) *58 and 64* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-7,9,34,35,42,46,50,54,59-62,65 and 66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed 1/26/09 in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's amendment and remarks filed 1/26/09 have been entered.

2. Claims 58 and 64 stand withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected species.

Claims 1, 2, 5-7, 9, 34, 35, 42, 46, 50, 54, 59-62, 65, and 66 read on the elected invention and are being acted upon.

3. In view of the instant amendment, the previous rejections under the second paragraphs of 35 U.S.C. 112 have been withdrawn. Additionally, the previous rejections under the first paragraph of 35 U.S.C. 112 for inadequate written description parts C) and F) have been withdrawn in view of the support now cited by Applicant.

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1, 5-7, 9, 34, 35, 50, 54, 59-62, 65, and 66 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Guo et al. (1994, IDS) in view of Sornasse et al. (1992, of record) and Young et al. (1990, of record).

As set forth previously, Guo et al. teaches a method for producing a plurality of hybrids comprising a bone marrow derived antigen-presenting B cell and a tumor cell (see particularly page 520, columns 2-3). The method comprises the providing of a tumor sample and an isolated autologous B cell, and the fusing of the cells with PEG to produce a plurality of hybrids (see particularly page

518, column 2). The reference teaches that the hybrids comprise cells that express both tumor-specific antigens and the machinery for antigen presentation, i.e., characteristics of both tumor cells and B cell APCs (see particularly page 518, column 1), that said hybrids are useful for the induction of an anti-tumor response in that they reduce the number of tumor cells upon administration to a subject (see particularly page 518, column 3). The reference further teaches that the hybrids were selected on the basis of a tumor cell surface marker and a B cell surface marker (see particularly page 518, column 3).

The reference teaching differs from the claimed invention only in that it does not teach the use of a DC as the antigen presenting component of the hybrid nor the isolation of said DCs from blood.

Sornasse et al. teaches that, while both B cells and DCs are capable of inducing IL2 secretion *in vitro*, DCs induce a more vigorous response, including a Th1 response, *in vivo* (see particularly pages 16-17, Results). The reference teaches the superiority of DCs over B cells for *in vivo* use, "Our data emphasize the main role of DC in initiating primary responses *in vivo*" (see page 18, column 1). Note that the DCs of the reference comprise splenic DCs which would include bone marrow derived DCs, lymphoid DCs, and myeloid DCs.

Young et al. teaches the routine isolation of DCs from human PBMC (peripheral blood mononuclear cells) (see page 1316, *PBMC and Preparation of Leukocyte Subpopulations*)

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to produce the hybrids of Guo et al., by the method of Guo et al., substituting a DC for the B cell in said hybrids, as taught by Sornasse et al, said DCs being isolated from human blood, as taught by Young et al. One of ordinary skill in the art at the time of the invention would have been motivated to make said substitution because, while both B cells and DCs are capable of inducing IL2 secretion *in vitro*, DCs induce a more vigorous response, including a Th1 response, *in vivo*, as taught by Sornasse et al. "Our data emphasize the main role of DC in initiating primary responses *in vivo*". Note that the additional limitations such as preparing a primary cell culture of the tumor cells comprises only an obvious and necessary step when said culture is not readily available as it was for Guo et al. Note, however, the BERH-2 tumor cells of Guo et al. derive from a hepatocarcinoma thus, said cells were previously the "primary culture" of tumor cells as set forth in the claims. Finally note that Young et al. teaches the routine use of human blood as a convenient source of DCs.

Applicant's arguments, filed 1/26/09, have been fully considered but they are not persuasive. Applicant argues that the amended claims no longer recite a method employing DCs autologous to a patient whereas the Guo et al. and Sornasse et al. references teach only the use of syngeneic DCs.

The instant claims simply recite a method of producing DC/tumor cell hybrids. The actual method steps recite only "providing", "fusing" and "selecting". Additionally, the DCs must be allogeneic in reference to some patient, while the tumor cells may be either autologous or allogeneic to said patient. Consider the hypothetical case of patient A and patient B. If

patient A's DCs are fused to patient A's tumor cells then both the DCs and tumor cells are allogeneic to patient B and the resulting method of producing a DC/tumor hybrid meets the limitations of the claims.

Applicant argues that it would not be obvious to substitute a DC for a B cell.

Adequate motivation for the substitution is set forth in the reference - DCs can be superior to B cells for antigen presentation.

Applicant argues that the hybrids of the instant claims are not exogenously pulsed with antigen.

Applicant's argument is irrelevant because "non-pulsing" is not a limitation of the claimed method. Proper motivation to produce DC/tumor hybrids has been established. Additionally, there is every expectation that the hybrids produced by the combined method of the combined references would function identically to the hybrids of the instant specification.

Applicant argues that Sornasse et al. teaches away from combing the references.

Sornasse et al. does not teach away from producing DC/tumor hybrids. A reference is said to "teach away" from a claimed invention when it "suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the Applicant" *(In re Gurley,* 27 F.3d *551,553,* 31 USPQ2d 1130, 1131 (Fed. Cir. 1994)). That is not the case here. Sornasse et al. makes no mention of DC/tumor hybrids, thus, there is nothing in the reference's disclosure that suggests that substituting a dendritic cell for a B cell in Guo's hybrids would be unlikely to be productive. Whether or not said hybrids would have been expected to have been able to process and present antigens is irrelevant because the hybrids could just as easily have been antigen pulsed.

6. Claims 2, 42, and 46, stand rejected under 35 U.S.C. 103(a) as being unpatentable over Guo et al. (1994, IDS) in view of Sornasse et al. (1992, of record) and Young et al. (1990, of record), as applied to Claims 1, 5-7, 9, 34, 35, 50, 54, 59-62,

65, and 66 above, and in further view of U.S. Patent No. 5,851,756 (of record).

As set forth previously, Guo et al., Sornasse et al., and Young et al. have been discussed, supra. The references differ from the claimed invention in that they do not teach the induction of DC characteristics before using said hybrids, nor the induction of said characteristics using GM-CSF.

The '756 patent teaches the induction of DC characteristics using GM-CSF (see particularly Example I). The reference further teaches that DC exist in relatively small numbers in blood, thus the induction of DC (and thus, DC characteristics) in GM-CSF before use provides a method to increase the number of said DCs (see particularly column 4, line 63 - column 5, line 9).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to produce the hybrids/hybridomas of Guo et al., Sornasse et al., and Young et al., by the method of Guo et al., substituting a DC induced with GM-CSF before use, as taught by the '756 patent, for the B cell in said hybrids. One of ordinary skill in the art at the time of the invention would have been motivated to induce DC (and thus, DC characteristics) with GM-CSF before use because DC exist in relatively small numbers in blood, thus the induction of DC in GM-CSF before use provides a method to increase the number of said DCs, as taught by the '756 patent.

See the Examiner's response to Applicant's arguments above.

7. Claims 50 and 54 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Guo et al. (1994, IDS) in view of Sornasse et al. (1992, of record) and Young et al. (1990, of record), as applied to Claims 1, 5-7, 9, 34, 35, 50, 54, 59-63, 65, and 66 above, and in further view of U.S. Patent No. 5,637,483 (of record).

As set forth previously, Guo et al., Sornasse et al., and Young et al. have been discussed, supra. The references differ from the claimed invention in that they do not teach the treatment of the hybrids with irradiation before using to prevent proliferation.

The '483 patent teaches the treatment of a tumor cell-containing anti-tumor vaccine with irradiation before using to prevent proliferation (see particularly column 3, lines 65-67 and column 14, lines 3-4).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to produce the hybrids of Guo et al., Sornasse et al., and Young et al., by the method of Guo et al. and employ irradiation before using, as taught by the '483 patent. One of ordinary skill in the art at the time of the invention would have been motivated to treat the hybrids/hybridomas with irradiation before using to prevent proliferation, as taught by the '483 patent.

See the Examiner's response to Applicant's arguments above.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1, 7, 9, 10, 59, 60, and 66 stand/are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Breel et al. (1988, IDS).

As set forth previously, Breel et al. teaches a method of producing a plurality of DC/tumor cell hybrids comprising providing a sample of tumor (SP2/0 myeloma cells, necessarily obtained from cell culture), providing isolated autologous (all cells are autologous to their source) lymph node DCs, and fusing the DCs with the tumor cells by a standard hybridoma fusion protocol (which would include PEG fusion and HAT selection) to produce a plurality of hybrids (see particularly Materials and Methods, page 168). The reference further teaches the selecting of a hybrid which exhibits a DC cell surface marker (NLDC-145) (see particularly Results, page 170). Note that the recitation of "providing a sample of a tumor *against which a response is needed*" is not considered to comprise an actual method step. The recitation of producing … cell hybrids *which induce an anti-tumor response when provided to a patient causing a reduction of the number of tumor cells in said patient*" is considered to be an inherent property of the hybrids.

Applicant's arguments, filed 1/26/09, have been fully considered but they are not persuasive. Applicant argues that the reference teaches the production of syngeneic hybrids.

As set forth in Section 5 above, syngeneic, allogeneic, and autologous are relevant only with a frame of reference. While the hybrids of Breel et al. may be syngeneic (essentially autologous) to a Balb/c mouse ($H\text{-}2^d$), they are allogeneic to a C57BL/10 mouse ($H\text{-}2^b$).

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1, 2, 5-7, 9, 34, 35, 42, 46, 50, 54, 59-62, 65, and 66 stand rejected under 35 U.S.C. 112, first paragraph, as the

specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a rejection for inadequate written description due to the introduction of new matter into the claims.

As set forth previously, The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically, the recitation of:

A) The method of Claim 1 comprising producing a plurality of DC/tumor cell hybrids:

a) for "a reduction of the number of tumor cells in a patient",

b) comprising the "allogeneic" DCs of step (a),

c) comprising the "allogeneic tumor cell characteristic of the same cancer type with respect to said patient" of step (b),

d) comprising selecting hybrids "that exhibit DC markers, TAAs and the capacity to activate naïve T cells in vitro that can recognize the cancer cells of step (b)".

B) The method of Claim 9 comprising producing a fused cell product "using PEG".

D) The method of Claim 59 comprising "a tumor cell line having at least one TAA in common with said tumor sample".

E) The method of Claim 65 comprising "an allogeneic tumor cell with respect to the patient, and has one or more TAAs in common with that of said autologous tumor cell".

Regarding A), a), Applicant cites original Claim 1 and again cites pages 15 and 60 of the specification. The disclosure of pages 15 and 60 has been addressed previously, see the Final Office action of 9/08/05. While original Claim 1 did recite the limitation necessitating the rejection set forth above, original Claim 1 is not "original" to parent applications 09/951,849 nor 09/049,502, of which the instant application claims to be a Divisional application and a Continuation application, respectively. Thus, the limitations of the claim must find support in the specification common to the three applications or the instant application must be filed as a Continuation-In-Part (CIP). As support for the limitation has not been found, and the instant application has not been filed as a CIP, the limitation is considered to comprise the introduction of new matter into the claims.

Regarding B), Applicant cites original Claim 9 and again cites Examples 3, 9, and 12 of the specification. Examples 3, 9, and 12 have been addressed previously, see the Final Office action of 9/08/05. Regarding the citing of original Claim 9, the same issue set forth in the previous paragraph applies to this limitation.

Regarding the limitations of C)-F), they have not been found in the instant specification.

Applicant's arguments, filed 1/26/09, have been fully considered but they are not persuasive. Applicant argues that Claim 1 is part of the instant specification as filed.

Applicant appears to argue that the instant application is not a divisional application, but rather a continuation in part application of parent application 09/951,849. If the instant application is not actually a divisional application of parent application 09/951,849 then the claims may not be afforded the parent application's priority date. Additionally, a new oath or declaration will be required.

Certainly Claim 1 of the instant application is considered part of the instant application as filed (though it now bears little resemblance to Claim 1 as filed, except for the preamble). But if the instant application is a divisional of parent application 09/951,849, which itself is a continuation of application 09/049,502, then support for the claims as now recited must be found in all 3 applications (because they must be identical).

NOTE: Applicant again confusingly cites support for claim limitations which have not been rejected. This support will not be addressed.

Applicant cites page 60 of the specification in support of, "a reduction of the number of tumor cells in a patient".

Page 60 discloses the results of Example 12 wherein the administration of a specific hybrid prevented the growth of a P815 mastocytoma in experimental mice. This disclosure clearly cannot support the generic claim to, "a reduction of the number of tumor cells in a patient", which encompasses *any* tumors in *any* patient.

Applicant cites original Claim 9 (and other cites) in the '502 application in support of "allogeneic DCs".

The cites only disclose HLA-compatible allogeneic DCs.

Applicant cites original Claim 9 and page 25 in the '502 application in support of "allogeneic tumor cell characteristic of the same cancer type with respect to said patient" of step".

The limitation simply is not found in Clam 9 nor page 25 of the '502 application.

Applicant cites original Claims 19 and 20 and page 59 in the '502 application in support of, "that exhibit DC markers, TAAs and the capacity to activate naïve T cells *in vitro* that can recognize the cancer cells of step (b)"

The method of Claims 19 and 20 of the '502 application employ "an established cell line comprising immortal human tumor cells". This is not the method of the instant claims which employs *any* tumor cells. Page 59 again discloses the results of an experiment employing P815 mastocytoma cells which, again are not representative of the generic tumor cells of the claims.

Applicant cites Examples 3, 9, and 12 in support of the limitation of producing a fused cell product "using PEG".

The disclosure of the specific examples is insufficient to support the generic method of the instant claims.

Applicant again cites Example 12 in support of, "a tumor cell line having at least one TAA in common with said tumor sample".

Again, Example 12 discloses only the P815 mouse mastocytoma cell line. Said single cell line provides insufficient support for the generic limitation of the claim.

Applicant cites pages 29-30 (embodiments J-M) in support of "an allogeneic tumor cell with respect to the patient, and has one or more TAAs in common with that of said autologous tumor cell".

The specific limitations of the claim have not been found in any of the embodiments".

12. No claim is allowed.

13. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara, Ph.D. can be reached on (571) 272-0878.

15. **Please Note:** Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/G.R. Ewoldt/
G.R. Ewoldt, Ph.D.
Primary Examiner
Technology Center 1600